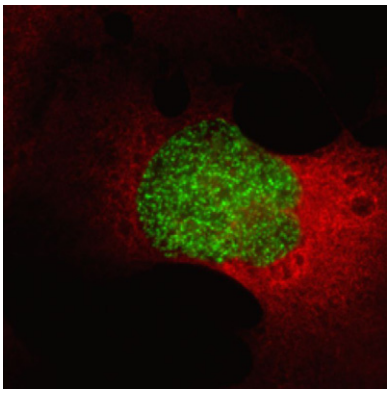
Select: Cell Cycle

Cell

The phases of the cell cycle must be exquisitely timed and tightly regulated in order to ensure proper chromosome replication and segregation and cell division. New findings described in this issue's Select address key regulatory events in the cell cycle and reveal potential clinical outcomes of errors in these processes.



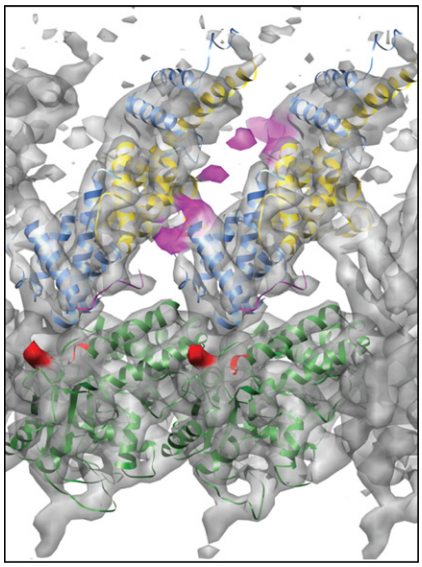
Re-replicating G2 cells (cyclin B1, red; EdU, green). Image courtesy of E. Julien.

An Epigenetic License to Replicate

Chromosome replication needs to occur once and only once during the cell cycle to produce daughter cells with accurate genetic content. Licensing of replication origins is one form of DNA synthesis regulation, in which origins are loaded with pre-replication complex (RC) proteins during the end of M phase and throughout G1. Without this licensing event, replication origins cannot be activated. New findings from Tardat et al. identify the methyltransferase PR-Set7—and the histone modification that it catalyzes, methylation of histone H4 lysine 20 (H4K20me1)—as a key regulator of the onset of licensing in mammalian cells. The authors show that PR-Set7 and H4K20me1 levels are cell cycle regulated—both are high during M and G1 phases, dropping in S when synthesis begins—and that proteasomal degradation of PR-Set7 is needed to prevent DNA re-replication. The authors also show that silencing PR-Set7 leads to decreased chromatin loading of pre-RC proteins and reduced origin firing during S phase, whereas targeting PR-Set7 to nonorigin sites on the chromatin is sufficient to induce H4K20me1 and the assembly of pre-RC proteins. Future studies are needed to investigate how H4K20me1 facilitates chromatin loading of pre-RC proteins.

M. Tardat et al. (2010). Nat. Cell Biol. Published online October 17, 2010. 10.1038/ncb2113.

Getting a Toehold on Microtubules



Two Ndc80 molecules (blue and yellow; N terminus, magenta) binding tubulin (green; C terminus, red). Image courtesy of E. Nogales.

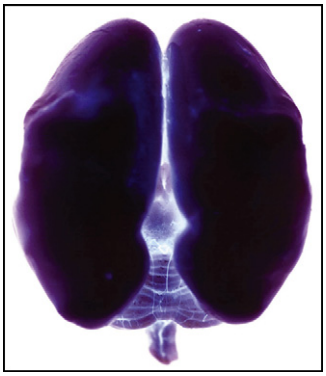
The ability of the kinetochore to maintain an attachment between chromosomes and microtubules is necessary for proper chromosomal segregation during anaphase. The Ndc80 complex is known to be a key regulatory site for microtubule attachment, but, given the highly dynamic process of microtubule assembly and disassembly occurring during segregation, it has been a challenge to identify how the Ndc80 complex physically holds on to such a rapidly changing structure. Alushin et al. address this using cryo-electron microscopy to better reveal the metazoan Ndc80 complex bound to microtubules. The authors find that the Ndc80 complex binds both α- and β-tubulin monomers and identify a "toe"—a short section of the NDC80 protein that recognizes a site between two tubulin monomers, a hinge point for tubulin bending. The toe appears to prefer binding straight tubulin, suggesting that it could act as a sensor for tubulin conformation. At the same time, the N terminus of NDC80 allows high-affinity microtubule binding and appears to mediate self-assembly of Ndc80 complexes in a manner that is modulated via phosphorylation by Aurora B kinase. The authors propose a model in which phosphorylated Ndc80 complexes bind a microtubule and spindle forces then pull the bound complex out of the Aurora B kinase phosphorylation zone. The resulting dephosphorylation of NDC80 results in high-affinity clusters forming in linear arrays along the microtubule. This cluster arrangement is consistent with a biased diffusion model of kinetochore attachment and movement. On a shrinking microtubule, the Ndc80-microtubule interaction would be reduced due to conformational changes in tubulin at the disassembling or depolymerizing end, and the cluster would diffuse along the microtubules toward the pole, thereby moving the chromosome in that direction.

*G.M. Alushin et al. (2010). Nature **467**, 805–810.*

Mounting Tension in Lead-Up to Fateful Decision

Asymmetric cell division, which generates daughter cells with different developmental fates, is often achieved through asymmetric positioning of the mitotic spindle. However, some dividing cells start out with a centered spindle that becomes displaced during anaphase. This progressive asymmetry has been postulated to arise from greater elongation of microtubules on one side of the spindle. New findings from Ou et al. suggest that nonmuscle myosin II might also play a role. The authors show that in the QR.a neuroblast of *Caenorhabditis elegans*, myosin II becomes asymmetrically distributed during anaphase, concentrating at the anterior side of the cleavage furrow. Consequently, the anterior membrane becomes less dynamic and shrinks inward, whereas the posterior membrane expands like a balloon, suggesting that cortical tension and contractile forces driven by myosin II could be a factor in developing asymmetry. The authors also used CALI (chromophore-assisted laser inactivation) to specifically inactivate myosin II at the anterior membrane and find that this increases the size of the anterior daughter cell and can alter its fate from apoptosis to differentiation into a neuron-like cell. Future work is needed to better understand the respective contributions of microtubule elongation, myosin polarization, and perhaps other unknown mechanisms to the regulation of asymmetric division and cell fate.

G. Ou et al. (2010). Science. Published online September 30, 2010. 10.1126/science.1196112.



Photograph of human microcephalic brain. Image courtesy of C. Walsh.

Spindle Position, a Neuronal Mover and Maker

Human microcephaly is a neurodevelopmental disorder characterized by a small brain, fewer surface ridges, and reduced cortical neuron numbers. Two recent papers used linkage analysis and genome capture in affected families to identify *WDR62* as a common cause of genetic microcephaly and characterized the WDR62 protein as a spindle pole protein expressed in mitotic neural precursors. After sequencing affected individuals to identify specific disease-causing mutations, Nicholas et al. expressed mutant WDR62 in HeLa cells and showed that the normal accumulation of the protein at the spindle poles during mitosis is disrupted. Given the phenotype of reduced neuron numbers and small brain seen in microcephaly, one possibility the authors suggest is that WDR62 could be involved in proper positioning of the mitotic spindle and cleavage furrow, such that mutant WDR62 results in insufficient symmetric divisions—needed to produce neural precursors—early in cortical development. In agreement, Yu et al. show that the brain of an affected individual has profound cortical defects, with thin sparse cortical layers and aberrant repositioning of neurons to subcortical regions, suggesting deficits in neurogenesis and migration. Further description of the specific role of WDR62 at the spindle will clarify how it is involved in cerebral development and aid in our understanding of the etiology of microcephaly.

A.K. Nicholas et al. (2010). Nat. Genet. Published online October 3, 2010. 10.1038/ng.682.

T.W. Yu et al. (2010). Nat. Genet. Published online October 3, 2010. 10.1038/ng.683.

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